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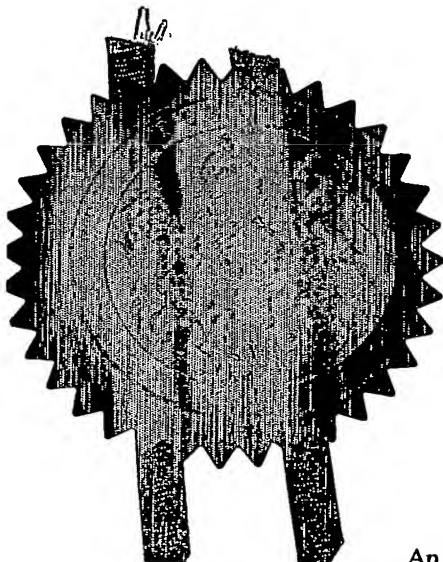
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The Patent Office

Cardiff Road
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1. Your reference

RJW/CP6131742

2. Patent application number

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0311195.2

15 MAY 2003

3. Full name, address and postcode of the or of each applicant (underline all surnames)

CHROMA THERAPEUTICS LIMITED
92 Milton Park
Abingdon
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OX14 4RY

Patents ADP number (*if you know it*)

If the applicant is a corporate body, give the country/state of its incorporation

8280414002
England

4. Title of the invention

GLYOXALASE INHIBITORS

5. Name of your agent (*if you have one*)

"Address for service" in the United Kingdom to which all correspondence should be sent (*including the postcode*)

MEWBURN ELLIS
York House
23 Kingsway
London WC2B 6HP

Patents ADP number (*if you know it*)

109006

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and (*if you know it*) the or each application number

Country

Priority application number
(*if you know it*)

Date of filing
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7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application

Date of filing
(*day / month / year*)

8. Is a statement of inventorship and of right to grant of a patent required in support of this request? (*Answer 'Yes' if:*

YES

- a) any applicant named in part 3 is not an inventor, or
 - b) there is an inventor who is not named as an applicant, or
 - c) any named applicant is a corporate body.
- See note (d))

Patents Form 1/77

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Priority documents

Translations of priority documents

Statement of inventorship and right to grant of a patent (*Patents Form 7/77*)

Request for preliminary examination and search (*Patents Form 9/77*)

Request for substantive examination (*Patents Form 10/77*)

Any other documents
(please specify)

11. I/We request the grant of a patent on the basis of this application.

Signature

Mervyn Ellis

Date

15 May 2003

12. Name and daytime telephone number of person to contact in the United Kingdom

ROBERT WATSON
020 7240 4405

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GLYOXALASE INHIBITORS

This invention relates to compounds which are glyoxalase I inhibitors, pharmaceutical compositions comprising such compounds, and the use of such compositions and compounds to treat various conditions alleviated by the inhibition of glyoxalase I.

10 Background to the invention

Methyl glyoxal (MG) is an endogenous cytotoxic agent that is formed in cells as a consequence of glycolysis. The glyoxalase system converts 2-oxoaldehydes such as MG into the corresponding 2-hydroxy acid in two consecutive steps.

15 MG is converted to D-lactate via the intermediate S-D-lactoylglutathione. The glyoxalase system comprises two enzymes, glyoxalase I and glyoxalase II. Glyoxalase I is the rate limiting enzyme, and catalyses the formation of S-D-lactoylglutathione from the hemithioacetal formed non-enzymatically from MG and reduced glutathione (GSH).

20 Glyoxalase II catalyses the hydrolysis of S-D-lactoylglutathione to D-lactate, reforming the GSH consumed in the glyoxalase I-catalysed reaction (Thornalley et al., *Crit. Rev. Oncol. Haematol.* 20, 99 (1995)).

25 High levels of MG form DNA adducts and are generally toxic to cells. Cells having high glycolytic rates such as tumour cells and certain parasites have increased levels of glyoxalase I, which is believed to be the major

30 detoxification pathway for MG. Glyoxalase-I levels were shown to be higher in 38 human cancer cell lines than in normal cells (Sakamoto et al., *Clin. Cancer Res.* 7, 2513 (2001)). Elevated glyoxalase I levels were observed in the following human cancer types: lung (Sakamoto et al., *ibid.*),

prostate (Sakamoto et al., *ibid.*; Davidson et al., *J. Urol.*
161, 690 (1999); Samadi et al., *Urology* 57, 183 (2001)),
colon (Ranganathan et al., *Biochim. Biophys. Acta* 1182, 311
(1993)), leukemia (Sakamoto et al., *Blood* 95, 3214 (2000))
5 and breast (Rulli et al., *Breast Canc. Res. Treat* 66, 67
(2001)). Agents that lead to an accumulation of MG, such as
glyoxalase inhibitors, might be expected to exert an anti-
tumor action (Thornalley et al., *Gen. Pharmacol.* 27, 565
(1996)) and are therefore likely to have a beneficial effect
10 on patients suffering from various forms of cancer.

Prototype peptidic glyoxalase I inhibitors have been
synthesised, based on knowledge of the substrate of
glyoxalase I, i.e. the hemithioacetal formed from MG and GSH
15 (Johansson et al., *Mol. Pharmacol.* 57, 619 (2000);
Thornalley et al. *J. Med. Chem.* 39, 3409 (1996); Kalsi et
al., *J. Med. Chem.* 42, 3981 (2000); Sharkey et al., *Cancer*
Chemother. Pharmacol. 46, 156 (2000)). Such inhibitors have
been shown to acutely increase MG levels and induce
20 apoptosis in cancer cells. Additionally they have been shown
to exert anti-cancer effects *in vivo*, both on their own and
synergising with existing cytotoxic agents (Thornalley et
al., *Biochem. Pharmacol.* 51, 1365 (1996); Sakamoto et al.,
Blood 95, 3214 (2000); Sharkey et al., *ibid.*). Moreover,
25 there is increasing evidence that tumour cell resistance to
certain cytotoxics (adriamycin, etoposide) may result, in
part, from the over-activity of glyoxalase I (Sakamoto et
al., *Blood* 95, 3214 (2000); Johansson et al., *ibid.*).

30 Known glyoxalase I inhibitor compounds are generally
peptidic and require esterification to gain access to the
interior of the cell where glyoxalase I is found. It is
therefore desirable to find classes of glyoxalase I

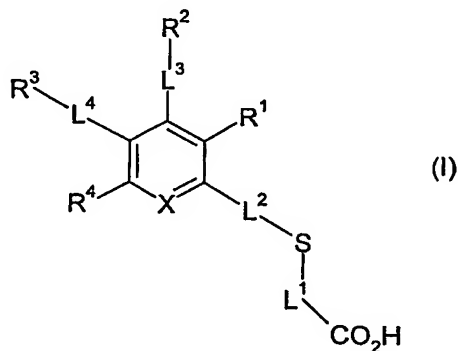
inhibitor compounds which are non-peptidic and hence have greater potential as therapeutic agents.

US Patent 4,898,870 describes pyrroloquinoline quinone
5 compounds in relation to glyoxalase I inhibition, although
no activity data for glyoxalase I inhibition is disclosed.
WO 99/35128 is related to competitive inhibitor compounds of
glyoxalase I, and a method of generating such inhibitors
inside tumour cells using an acyl-interchange reaction
10 between a membrane-permeable prodrug and intracellular
glutathione.

The invention provides further classes of glyoxalase I
inhibitor compounds which are non-peptidic, and therefore
15 have greater potential as therapeutic agents.

Summary of the invention

A first aspect of the present invention provides a compound
of formula I:



(I)

20

wherein

X is N or CH;

R¹ is H, cyano, halo, hydroxy, hydroxamic acid,
sulfhydryl or -NH₂; or C₁₋₄ alkyl optionally substituted by
25 cyano, halo, hydroxy, hydroxamic acid, sulfhydryl or -NH₂;
or -OR, -NHR, -NR₂ or -SR wherein R is C₁₋₄ alkyl optionally
substituted by cyano, halo, hydroxy, hydroxamic acid,

sulphydryl or -NH_2 ;

~~R^2 is H, CF_3 , or optionally substituted C_{5-6} aryl, C_{3-7} cycloalkyl, C_{5-7} heterocyclyl or together with R^3 an optionally substituted C_{3-4} alkylene group wherein L^3 and L^4 are single bonds thus forming a C_{5-6} ring fused with the aromatic ring to which L^3 and L^4 are attached;~~

R^3 is H; or optionally substituted C_{5-6} aryl, C_{3-7} cycloalkyl, C_{5-7} heterocyclyl or together with R^2 an optionally substituted C_{3-4} alkylene group wherein L^3 and L^4 are single bonds thus forming a C_{5-6} ring fused with the aromatic ring to which L^3 and L^4 are attached;

R^4 is H; or optionally substituted C_{5-6} aryl or C_{5-7} heterocyclyl;

L^1 is optionally substituted C_{1-4} alkylene, C_{5-6} arylene, C_{1-4} alkylene- C_{5-6} arylene or $\text{-L}^5\text{N}(\text{R}^5)\text{L}^6\text{-}$, wherein L^5 and L^6 are independently selected from optionally substituted C_{1-4} alkylene and C_{5-6} arylene, and R^5 is H or C_{1-4} alkyl;

L^2 is a single bond; or optionally substituted C_{1-4} alkylene or $\text{-L}^7\text{C}(=\text{O})\text{L}^8\text{-}$, wherein L^7 and L^8 are independently selected from optionally substituted C_{1-4} alkylene and a single bond; and

L^3 and L^4 are independently selected from a single bond, optionally substituted C_{1-4} alkylene, $\text{-L}^9\text{YN}(\text{OH})\text{C}(=\text{O})\text{L}^{10}\text{-}$ and $\text{-L}^9\text{C}(=\text{O})\text{N}(\text{OH})\text{YL}^{10}\text{-}$, wherein L^9 and L^{10} are independently selected from optionally substituted C_{1-4} alkylene, C_{5-6} arylene, C_{1-4} alkylene- C_{5-6} arylene and a single bond, wherein Y is NH or a single bond;

or a pharmaceutically acceptable salt thereof for use in a method of therapy.

A second aspect of the present invention provides a pharmaceutical composition comprising a compound of formula I as defined in the first aspect or a pharmaceutically acceptable salt thereof together with a pharmaceutically

acceptable carrier or diluent.

A further aspect of the present invention provides the use of a compound of formula I or a pharmaceutically acceptable salt thereof in the preparation of a medicament for the treatment of a condition alleviated by inhibition of glyoxalase I.

Another aspect of the present invention provides a method of treating a condition which can be alleviated by inhibition of glyoxalase I, which method comprises administering to a patient in need of treatment an effective amount of a compound of formula I, or a pharmaceutically acceptable salt thereof.

Another aspect of the present invention provides novel compounds or salts, solvates and chemically protected forms thereof, and methods of synthesis thereof as described herein.

Conditions alleviated by inhibition of glyoxalase I are proliferative conditions. The term "proliferative condition" pertains to an unwanted or uncontrolled cellular proliferation of excessive or abnormal cells which is undesired, such as, neoplastic or hyperplastic growth, whether *in vitro* or *in vivo*.

Examples of proliferative conditions include, but are not limited to, benign, pre-malignant, and malignant cellular proliferation, including but not limited to, neoplasms and tumours (e.g., histocytoma, glioma, astrocytoma, osteoma), cancers (e.g., lung cancer, small cell lung cancer, gastrointestinal cancer, bowel cancer, colon cancer, breast carcinoma, ovarian carcinoma, prostate cancer, testicular

cancer, liver cancer, kidney cancer, bladder cancer,
~~pancreas cancer, brain cancer, sarcoma, osteosarcoma,~~
Kaposi's sarcoma, melanoma), leukemias, psoriasis, bone
diseases, fibroproliferative disorders (e.g., of connective
5 tissues), and atherosclerosis.

Any type of cell may be treated, including but not limited
to, lung, gastrointestinal (including, e.g., bowel, colon),
breast (mammary), ovarian, prostate, liver (hepatic), kidney
10 (renal), bladder, pancreas, brain, and skin.

Definitions

Cyano: The term "cyano", as used herein, pertains to the
monovalent moiety -CN.

15

Halo: The term "halo", as used herein, pertains to the
monovalent moiety -Y, wherein Y is a halogen atom. Examples
of halo groups include -F, -Cl, -Br, and -I.

20 Hydroxy: The term "hydroxy", as used herein, pertains to the
monovalent moiety -OH.

Hydroxamic acid: The term "hydroxamic acid", as used herein,
pertains to the monovalent moiety $-C(=O)NH(OH)$.

25

Sulfhydryl: The term "sulfhydryl", as used herein, pertains
to the monovalent moiety -SH.

C_{1-4} alkyl group: The term " C_{1-4} alkyl", as used herein,
30 pertains to a monovalent moiety obtained by removing a
hydrogen atom from a carbon atom of a non-cyclic hydrocarbon
compound having from 1 to 4 carbon atoms, and which may be
saturated or unsaturated.

Examples of saturated C₁₋₄ alkyl groups include methyl (C₁); ethyl (C₂); propyl (C₃), which may be linear (n-propyl) or branched (iso-propyl); butyl (C₄), which may be linear (n-butyl) or branched (iso-butyl, sec-butyl and tert-butyl).

5

Examples of unsaturated C₁₋₄ alkyl groups, which may be referred to as C₁₋₄ alkenyl (if they included a double bond) or C₁₋₄ alkynyl (if they include a triple bond) groups, include ethenyl (vinyl, -CH=CH₂), ethynyl (ethynyl, -C≡CH),
10 1-propenyl (-CH=CH-CH₃), 2-propenyl (allyl, -CH=CH-CH₂),
2-propynyl (propargyl, -CH₂-C≡CH), isopropenyl (-C(CH₃)=CH₂)
and butenyl (C₄).

C₃₋₇ Cycloalkyl: The term "C₃₋₇ cycloalkyl", as used herein,
15 pertains to an alkyl group which is also a cyclyl group;
that is, a monovalent moiety obtained by removing a hydrogen
atom from an alicyclic ring atom of a cyclic hydrocarbon
(carbocyclic) compound, which moiety has from 3 to 7 ring
atoms (unless otherwise specified).

20

Examples of saturated cycloalkyl groups include, but are not
limited to, those derived from: cyclopropane (C₃),
cyclobutane (C₄), cyclopentane (C₅), cyclohexane (C₆),
cycloheptane (C₇), norbornane (C₇), norpinane (C₇), norcarane
25 (C₇).

C₅₋₇ Heterocyclyl: The term "C₅₋₇ heterocyclyl", as used
herein, pertains to a monovalent moiety obtained by removing
a hydrogen atom from a ring atom of a heterocyclic compound,
30 which moiety has from 5 to 7 ring atoms, of which from 1 to
4 are ring heteroatoms.

In this context, the prefix C₅₋₇ denotes the number of ring
atoms, or range of number of ring atoms, whether carbon

atoms or heteroatoms. For example, the term " C_{5-7} heterocyclyl" as used herein, pertains to a heterocyclyl group having 5 to 7 ring atoms. Examples of groups of heterocyclyl groups include C_{5-7} heterocyclyl and C_{5-6} heterocyclyl.

Examples of (non-aromatic) monocyclic heterocyclyl groups include, but are not limited to, those derived from:

- 10 N_1 : pyrrolidine (tetrahydropyrrole) (C_5), pyrroline (e.g., 3-pyrroline, 2,5-dihydropyrrole) (C_5), 2H-pyrrole or 3H-pyrrole (isopyrrole, isoazole) (C_5), piperidine (C_6), dihydropyridine (C_6), tetrahydropyridine (C_6), azepine (C_7);
- 15 O_1 : oxolane (tetrahydrofuran) (C_5), oxole (dihydrofuran) (C_5), oxane (tetrahydropyran) (C_6), dihydropyran (C_6), pyran (C_6), oxepin (C_7);
- S_1 : thiolane (tetrahydrothiophene) (C_5), thiane (tetrahydrothiopyran) (C_6), thiepane (C_7);
- O_2 : dioxolane (C_5), dioxane (C_6), and dioxepane (C_7);
- 20 O_3 : trioxane (C_6);
- N_2 : imidazolidine (C_5), pyrazolidine (diazolidine) (C_5), imidazoline (C_5), pyrazoline (dihydropyrazole) (C_5), piperazine (C_6);
- N_1O_1 : tetrahydrooxazole (C_5), dihydrooxazole (C_5),
- 25 tetrahydroisoxazole (C_5), dihydroisoxazole (C_5), morpholine (C_6), tetrahydrooxazine (C_6), dihydrooxazine (C_6), oxazine (C_6);
- N_1S_1 : thiazoline (C_5), thiazolidine (C_5), thiomorpholine (C_6);
- 30 N_2O_1 : 5,5-diazirine (C_6);
- O_1S_1 : oxathiole (C_5) and oxathiane (thioxane) (C_6); and,
- $N_1O_1S_1$: oxathiazine (C_6).

Examples of substituted (non-aromatic) monocyclic heterocyclyl groups include those derived from saccharides, in cyclic form, for example, furanoses (C_5), such as arabinofuranose, lyxofuranose, ribofuranose, and xylofuranse, and pyranoses (C_6), such as allopyranose, altropyranose, glucopyranose, mannopyranose, gulopyranose, idopyranose, galactopyranose, and talopyranose.

Examples of heterocyclyl groups which are also heteroaryl groups are described below with aryl groups.

C_{5-6} aryl: The term " C_{5-6} aryl", as used herein, pertains to a monovalent moiety obtained by removing a hydrogen atom from an aromatic ring atom of an aromatic compound, which moiety has from 5 to 6 ring atoms (unless otherwise specified). In this context, the prefix C_{5-6} denotes the number of ring atoms, or range of number of ring atoms, whether carbon atoms or heteroatoms. For example, the term " C_{5-6} aryl," as used herein, pertains to an aryl group having 5 or 6 ring atoms.

The ring atoms may be all carbon atoms, as in "carboaryl groups." Examples of carboaryl groups include C_{5-6} carboaryl, C_5 carboaryl, and C_6 carboaryl.

Examples of carboaryl groups include, but are not limited to, those derived from benzene (i.e., phenyl) (C_6).

Alternatively, the ring atoms may include one or more heteroatoms, as in "heteroaryl groups." Examples of heteroaryl groups include C_{5-6} heteroaryl, C_5 heteroaryl, and C_6 heteroaryl.

Examples of monocyclic heteroaryl groups include, but are not limited to, those derived from:

- N₁: pyrrole (azole) (C₅), pyridine (azine) (C₆);
- O₁: furan (oxole) (C₅);
- 5 S₁: thiophene (thiole) (C₅);
- N₁O₁: oxazole (C₅), isoxazole (C₅), isoxazine (C₆);
- N₂O₁: oxadiazole (furazan) (C₅);
- N₃O₁: oxatriazole (C₅);
- N₁S₁: thiazole (C₅), isothiazole (C₅);
- 10 N₂: imidazole (1,3-diazole) (C₅), pyrazole (1,2-diazole) (C₅), pyridazine (1,2-diazine) (C₆), pyrimidine (1,3-diazine) (C₆) (e.g., cytosine, thymine, uracil), pyrazine (1,4-diazine) (C₆);
- N₃: triazole (C₅), triazine (C₆); and,
- 15 N₄: tetrazole (C₅).

Heterocyclic groups (including heteroaryl groups) which have a nitrogen ring atom in the form of an -NH- group may be N-substituted, that is, as -NR-. For example, pyrrole may be N-methyl substituted, to give N-methylpyrrole. Examples of N-substitutents include, but are not limited to C₁₋₄ alkyl, C₅₋₇ heterocyclyl, C₅₋₆ aryl, and acyl groups.

25 The term "bidentate substituents," as used herein, pertains to substituents which have two points of covalent attachment, and which act as a linking group between two other moieties.

30 C₁₋₄ alkylene: The term "C₁₋₄ alkylene" as used herein, pertains to a bidentate moiety obtained by removing two hydrogen atoms from opposite ends of a linear hydrocarbon compound having from 1 to 4 carbon atoms (unless otherwise specified), and which may be saturated, partially unsaturated, or fully unsaturated. Thus, the term

"alkylene" includes the sub-classes alkenylene, alkynylene, etc., discussed below.

5 In this context, the prefix C₁₋₄ denotes the number of carbon atoms, or range of number of carbon atoms. For example, the term "C₁₋₄ alkylene" as used herein, pertains to an alkylene group having from 1 to 4 carbon atoms.

10 Examples of saturated C₁₋₄ alkylene groups include, but are not limited to, -(CH₂)_n- where n is an integer from 1 to 4, for example, -CH₂- (methylene), -CH₂CH₂- (ethylene), -CH₂CH₂CH₂- (propylene), and -CH₂CH₂CH₂CH₂- (butylene).

15 Examples of partially unsaturated C₁₋₄ alkylene groups include, but are not limited to, -CH=CH- (vinylene), -CH=CH-CH₂-, -CH₂-CH=CH₂-, -CH=CH-CH₂-CH₂-, -CH=CH-CH=CH-.

20 C₅₋₆ arylene: The term "C₅₋₆ arylene", as used herein, pertains to a bidentate moiety obtained by removing two hydrogen atoms, one from each of two different aromatic ring atoms of an aromatic compound, which moiety has from 5 to 6 ring atoms (unless otherwise specified).

25 In this context, the prefix C₅₋₆ denotes the number of ring atoms, or range of number of ring atoms, whether carbon atoms or heteroatoms. For example, the term "C₅₋₆ arylene" as used herein, pertains to an arylene group having 5 or 6 ring atoms. Examples of groups of arylene groups include C₅₋₆ arylene, C₅ arylene, and C₆ arylene.

30

The ring atoms may be all carbon atoms, as in "carboarylene groups" (e.g., C₅₋₆ carboarylene).

Examples of C₅₋₆ arylene groups which do not have ring heteroatoms (i.e., ~~C₅₋₆ carboarylene groups~~) include, but are not limited to, those derived from the compounds discussed above in regard to carboaryl groups.

Alternatively, the ring atoms may include one or more heteroatoms, as in "heteroarylene groups" (e.g., C₅₋₆ heteroarylene).

10 Examples of C₅₋₆ heteroarylene groups include, but are not limited to, those derived from the compounds discussed above in regard to heteroaryl groups.

15 C₁₋₄ alkylene-C₅₋₆ arylene: The term "C₁₋₄ alkylene-C₅₋₆ arylene", as used herein, pertains to a bidentate moiety comprising a C₁₋₄ alkylene moiety, -C₁₋₄ alkylene-, linked to a C₅₋₆ arylene moiety, -C₅₋₆ arylene-, that is, -C₁₋₄ alkylene-C₅₋₆ arylene-.

20 Examples of C₁₋₄ alkylene-C₅₋₆ arylene groups include, for example, methylene-phenylene, ethylene-phenylene, propylene-phenylene, and ethenylene-phenylene (also known as vinylene-phenylene).

25 The phrase "optionally substituted", as used herein, pertains to a group, as above, which may be unsubstituted or which may be substituted by one of the following substituent groups or one of the groups listed above:

30 C₁₋₇ alkyl group: The term "C₁₋₇ alkyl", as used herein, pertains to a monovalent moiety obtained by removing a hydrogen atom from a carbon atom of a hydrocarbon compound having from 1 to 7 carbon atoms (unless otherwise specified), which may be aliphatic or alicyclic, and which

may be saturated, partially unsaturated, or fully unsaturated. Thus, the term "alkyl" includes the sub-classes alkenyl, alkynyl and cycloalkyl discussed below.

- 5 In this context, the prefixes (e.g. C₁₋₄, C₁₋₇, C₂₋₇, C₃₋₇, etc.) denote the number of carbon atoms, or range of number of carbon atoms. For example, the term "C₁₋₄ alkyl," as used herein, pertains to an alkyl group having from 1 to 4 carbon atoms. Examples of groups of alkyl groups include C₁₋₄ alkyl
10 ("lower alkyl") and C₁₋₇ alkyl.

Examples of saturated alkyl groups include, but are not limited to, methyl (C₁), ethyl (C₂), propyl (C₃), butyl (C₄),
15 pentyl (C₅), hexyl (C₆), heptyl (C₇).

Examples of saturated linear alkyl groups include, but are not limited to, methyl (C₁), ethyl (C₂), n-propyl (C₃),
n-butyl (C₄), n-pentyl (amyl) (C₅), n-hexyl (C₆), and n-
20 heptyl (C₇).

Examples of saturated branched alkyl groups include iso-propyl (C₃), iso-butyl (C₄), sec-butyl (C₄), tert-butyl (C₄), iso-pentyl (C₅), and neo-pentyl (C₅).

- 25 Cycloalkyl: The term "cycloalkyl", as used herein, pertains to an alkyl group which is also a cyclyl group; that is, a monovalent moiety obtained by removing a hydrogen atom from an alicyclic ring atom of a cyclic hydrocarbon (carbocyclic) compound, which moiety has from 3 to 20 ring atoms (unless
30 otherwise specified). Preferably, each ring has from 3 to 7 ring atoms.

Examples of saturated cycloalkyl groups include, but are not limited to, those derived from: cyclopropane (C₃),

cyclobutane (C₄), cyclopentane (C₅), cyclohexane (C₆),
~~cycloheptane (C₇), norbornane (C₇), norpinane (C₇), norcarane~~
(C₇), adamantane (C₁₀), and decalin (decahydronaphthalene)
(C₁₀).

5 Examples of saturated cycloalkyl groups, which are also
referred to herein as "alkyl-cycloalkyl" groups, include,
but are not limited to, methylcyclopropyl,
dimethylcyclopropyl, methylcyclobutyl, dimethylcyclobutyl,
10 methylcyclopentyl, dimethylcyclopentyl, methylcyclohexyl,
and dimethylcyclohexyl, menthane, thujane, carane, pinane,
bornane, norcarane, and camphene.

15 Examples of unsaturated cyclic alkenyl groups, which are
also referred to herein as "alkyl-cycloalkenyl" groups,
include, but are not limited to, methylcyclopropenyl,
dimethylcyclopropenyl, methylcyclobutenyl,
dimethylcyclobutenyl, methylcyclopentenyl,
dimethylcyclopentenyl, methylcyclohexenyl, and
20 dimethylcyclohexenyl.

25 Examples of cycloalkyl groups, with one or more other rings
fused to the parent cycloalkyl group, include, but are not
limited to, those derived from: indene (C₉), indan (e.g.,
2,3-dihydro-1H-indene) (C₉), tetraline (1,2,3,4-
tetrahydronaphthalene (C₁₀), acenaphthene (C₁₂), fluorene
(C₁₃), phenalene (C₁₃), acephenanthrene (C₁₅), aceanthrene
(C₁₆). For example, 2H-inden-2-yl is a C₉cycloalkyl group
with a substituent (phenyl) fused thereto.

30 Alkenyl: The term "alkenyl," as used herein, pertains to an
alkyl group having one or more carbon-carbon double bonds.
Examples of groups of alkenyl groups include C₂₋₄ alkenyl,
C₂₋₇ alkenyl, C₂₋₂₀ alkenyl.

Examples of unsaturated alkenyl groups include, but are not limited to, ethenyl (vinyl, $-\text{CH}=\text{CH}_2$), 1-propenyl ($-\text{CH}=\text{CH}-\text{CH}_3$), 2-propenyl (allyl, $-\text{CH}-\text{CH}=\text{CH}_2$), isopropenyl

5 ($-\text{C}(\text{CH}_3)=\text{CH}_2$), butenyl (C_4), pentenyl (C_5), and hexenyl (C_6).

Examples of unsaturated cyclic alkenyl groups, which are also referred to herein as "cycloalkenyl" groups, include, but are not limited to, cyclopropenyl (C_3), cyclobutenyl

10 (C_4), cyclopentenyl (C_5), and cyclohexenyl (C_6).

Alkynyl: The term "alkynyl," as used herein, pertains to an alkyl group having one or more carbon-carbon triple bonds.

Examples of groups of alkynyl groups include C_{2-4} alkynyl,

15 C_{2-7} alkynyl, C_{2-20} alkynyl.

Examples of unsaturated alkynyl groups include, but are not limited to, ethynyl (ethynyl, $-\text{C}\equiv\text{CH}$) and 2-propynyl (propargyl, $-\text{CH}_2-\text{C}\equiv\text{CH}$).

20

C_{3-7} heterocyclyl group: The term " C_{3-7} heterocyclyl", as used herein, pertains to a monovalent moiety obtained by removing a hydrogen atom from a ring atom of a heterocyclic compound, which moiety has from 3 to 7 ring atoms (unless otherwise

25 specified), of which from 1 to 4 are ring heteroatoms.

In this context, the prefixes (e.g. C_{3-7} , C_{5-6} etc.) denote the number of ring atoms, or range of number of ring atoms, whether carbon atoms or heteroatoms. For example, the term

30 " C_{5-6} heterocyclyl", as used herein, pertains to a heterocyclyl group having 5 or 6 ring atoms. Examples of groups of heterocyclyl groups include C_{3-7} heterocyclyl, C_{5-7} heterocyclyl.

Examples of monocyclic heterocyclyl groups include, but are not limited to, those derived from:

- N₁: aziridine (C₃), azetidine (C₄), pyrrolidine (tetrahydropyrrole) (C₅), pyrroline (e.g., 3-pyrroline, 2,5-dihydropyrrole) (C₅), 2H-pyrrole or 3H-pyrrole (isopyrrole, isoazole) (C₅), piperidine (C₆), dihydropyridine (C₆), tetrahydropyridine (C₆), azepine (C₇);
- O₁: oxirane (C₃), oxetane (C₄), oxolane (tetrahydrofuran) (C₅), oxole (dihydrofuran) (C₅), oxane (tetrahydropyran) (C₆), dihydropyran (C₆), pyran (C₆), oxepin (C₇);
- S₁: thiirane (C₃), thietane (C₄), thiolane (tetrahydrothiophene) (C₅), thiane (tetrahydrothiopyran) (C₆), thiopane (C₇);
- O₂: dioxolane (C₅), dioxane (C₆), and dioxepane (C₇);
- O₃: trioxane (C₆);
- N₂: imidazolidine (C₅), pyrazolidine (diazolidine) (C₅), imidazoline (C₅), pyrazoline (dihydropyrazole) (C₅), piperazine (C₆);
- N₁O₁: tetrahydrooxazole (C₅), dihydrooxazole (C₅), tetrahydroisoxazole (C₅), dihydroisoxazole (C₅), morpholine (C₆), tetrahydrooxazine (C₆), dihydrooxazine (C₆), oxazine (C₆);
- N₁S₁: thiazoline (C₅), thiazolidine (C₅), thiomorpholine (C₆);
- N₂O₁: oxadiazine (C₆);
- O₁S₁: oxathiole (C₅) and oxathiane (thioxane) (C₆); and,
- N₁O₁S₁: oxathiazine (C₆).

C₅₋₇ aryl: The term "C₅₋₇ aryl" as used herein, pertains to a monovalent moiety obtained by removing a hydrogen atom from an aromatic ring atom of an aromatic compound, which moiety has from 5 to 7 ring atoms (unless otherwise specified).

In this context, the prefixes (e.g. C₅₋₇, C₅₋₆ etc.) denote the number of ring atoms, or range of number of ring atoms, whether carbon atoms or heteroatoms. For example, the term "C₅₋₆ aryl" as used herein, pertains to an aryl group having 5 or 6 ring atoms. Examples of groups of aryl groups include C₅₋₇ aryl, C₅₋₆ aryl, C₅ aryl and C₆ aryl.

The ring atoms may be all carbon atoms, as in "carboaryl groups". Examples of carboaryl groups include C₅₋₇ carboaryl, C₅₋₆ carboaryl, C₅ carboaryl and C₆ carboaryl.

Examples of carboaryl groups include, but are not limited to, those derived from benzene (i.e. phenyl) (C₆).

Alternatively, the ring atoms may include one or more heteroatoms, as in "heteroaryl groups." Examples of heteroaryl groups include C₅₋₇ heteroaryl, C₅₋₆ heteroaryl, C₅ heteroaryl and C₆ heteroaryl.

Examples of monocyclic heteroaryl groups include, but are not limited to, those derived from:

N₁: pyrrole (azole) (C₅), pyridine (azine) (C₆);

O₁: furan (oxole) (C₅);

S₁: thiophene (thiole) (C₅);

N₁O₁: oxazole (C₅), isoxazole (C₅), isoxazine (C₆);

N₂O₁: oxadiazole (furazan) (C₅);

N₃O₁: oxatriazole (C₅);

N₁S₁: thiazole (C₅), isothiazole (C₅);

N₂: imidazole (1,3-diazole) (C₅), pyrazole.

(1,2-diazole) (C₅), pyridazine (1,2-diazine) (C₆), pyrimidine (1,3-diazine) (C₆) (e.g., cytosine, thymine, uracil), pyrazine (1,4-diazine) (C₆);

N₃: triazole (C₅), triazine (C₆); and,

N₄: tetrazole (C₅).

~~Heterocyclic groups (including heteroaryl groups)~~ which have a nitrogen ring atom in the form of an -NH- group may be N-substituted, that is, as -NR-. For example, pyrrole may be N-methyl substituted, to give N-methylpyrrole. Examples of N-substituents include, but are not limited to C₁₋₇alkyl, C₃₋₇ heterocyclyl, C₅₋₇ aryl, and acyl groups.

Halo: -F, -Cl, -Br, and -I.

10

Hydroxy: -OH.

Ether: -OR, wherein R is an ether substituent, for example, a C₁₋₇ alkyl group (also referred to as a C₁₋₇ alkoxy group, discussed below), a C₃₋₇ heterocyclyl group (also referred to as a C₃₋₇ heterocyclyloxy group), or a C₅₋₇ aryl group (also referred to as a C₅₋₇ aryloxy group), preferably a C₁₋₇ alkyl group.

C₁₋₇ alkoxy: -OR, wherein R is a C₁₋₇ alkyl group. Examples of C₁₋₇ alkoxy groups include, but are not limited to, -OMe (methoxy), -OEt (ethoxy), -O(nPr) (n-propoxy), -O(iPr) (isopropoxy), -O(nBu) (n-butoxy), -O(sBu) (sec-butoxy), -O(iBu) (isobutoxy), and -O(tBu) (tert-butoxy).

25

Oxo (keto, -one): =O.

Thione (thioketone): =S.

Imino (imine): =NR, wherein R is an imino substituent, for example, hydrogen, C₁₋₇ alkyl group, a C₃₋₇ heterocyclyl group, or a C₅₋₇ aryl group, preferably hydrogen or a C₁₋₇

30

alkyl group. Examples of ester groups include, but are not limited to, =NH, =NMe, =NEt, and =NPh.

Formyl (carbaldehyde, carboxaldehyde): -C(=O)H .

5

Acyl (keto): -C(=O)R , wherein R is an acyl substituent, for example, a C_{1-7} alkyl group (also referred to as C_{1-7} alkylacyl or C_{1-7} alkanoyl), a C_{3-7} heterocyclyl group (also referred to as C_{3-7} heterocyclylacyl), or a C_{5-7} aryl group (also referred to as C_{5-7} arylacyl), preferably a C_{1-7} alkyl group. Examples of acyl groups include, but are not limited to, -C(=O)CH_3 (acetyl), $\text{-C(=O)CH}_2\text{CH}_3$ (propionyl), $\text{-C(=O)C(CH}_3)_3$ (t-butyryl), and -C(=O)Ph (benzoyl, phenone).

10

15 Carboxy (carboxylic acid): -C(=O)OH .

Thiocarboxy (thiocarboxylic acid): -C(=S)SH .

Thiolocarboxy (thiolocarboxylic acid): -C(=O)SH .

20

Thionocarboxy (thionocarboxylic acid): -C(=S)OH .

Imidic acid: -C(=NH)OH .

25 Hydroxamic acid: -C(=O)NH(OH) .

Ester (carboxylate, carboxylic acid ester, oxycarbonyl):

-C(=O)OR , wherein R is an ester substituent, for example, a C_{1-7} alkyl group, a C_{3-7} heterocyclyl group, or a C_{5-7} aryl group, preferably a C_{1-7} alkyl group. Examples of ester groups include, but are not limited to, -C(=O)OCH_3 , $\text{-C(=O)OCH}_2\text{CH}_3$, $\text{-C(=O)OC(CH}_3)_3$, and -C(=O)OPh .

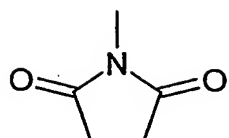
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Acyloxy (reverse ester): $-\text{OC}(=\text{O})\text{R}$, wherein R is an acyloxy substituent, for example, a C_{1-7} alkyl group, a C_{3-7} heterocyclyl group, or a C_{5-7} aryl group, preferably a C_{1-7} alkyl group. Examples of acyloxy groups include, but are not limited to, $-\text{OC}(=\text{O})\text{CH}_3$ (acetoxy), $-\text{OC}(=\text{O})\text{CH}_2\text{CH}_3$, $-\text{OC}(=\text{O})\text{C}(\text{CH}_3)_3$, $-\text{OC}(=\text{O})\text{Ph}$, and $-\text{OC}(=\text{O})\text{CH}_2\text{Ph}$.

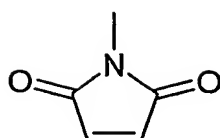
Oxycarboxyloxy: $-\text{OC}(=\text{O})\text{OR}$, wherein R is an ester substituent, for example, a C_{1-7} alkyl group, a C_{3-7} heterocyclyl group, or a C_{5-7} aryl group, preferably a C_{1-7} alkyl group. Examples of ester groups include, but are not limited to, $-\text{OC}(=\text{O})\text{OCH}_3$, $-\text{OC}(=\text{O})\text{OCH}_2\text{CH}_3$, $-\text{OC}(=\text{O})\text{OC}(\text{CH}_3)_3$, and $-\text{OC}(=\text{O})\text{OPh}$.

Amido (carbamoyl, carbamyl, aminocarbonyl, carboxamide): $-\text{C}(=\text{O})\text{NR}^1\text{R}^2$, wherein R^1 and R^2 are independently amino substituents, as defined for amino groups. Examples of amido groups include, but are not limited to, $-\text{C}(=\text{O})\text{NH}_2$, $-\text{C}(=\text{O})\text{NHCH}_3$, $-\text{C}(=\text{O})\text{N}(\text{CH}_3)_2$, $-\text{C}(=\text{O})\text{NHCH}_2\text{CH}_3$, and $-\text{C}(=\text{O})\text{N}(\text{CH}_2\text{CH}_3)_2$, as well as amido groups in which R^1 and R^2 , together with the nitrogen atom to which they are attached, form a heterocyclic structure as in, for example, piperidinocarbonyl, morpholinocarbonyl, thiomorpholinocarbonyl, and piperazinocarbonyl.

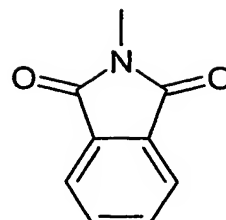
Acylamido (acylamino): $-\text{NR}^1\text{C}(=\text{O})\text{R}^2$, wherein R^1 is an amide substituent, for example, hydrogen, a C_{1-7} alkyl group, a C_{3-7} heterocyclyl group, or a C_{5-7} aryl group, preferably hydrogen or a C_{1-7} alkyl group, and R^2 is an acyl substituent, for example, a C_{1-7} alkyl group, a C_{3-7} heterocyclyl group, or a C_{5-7} aryl group, preferably hydrogen or a C_{1-7} alkyl group. Examples of acylamide groups include, but are not limited to, $-\text{NHC}(=\text{O})\text{CH}_3$, $-\text{NHC}(=\text{O})\text{CH}_2\text{CH}_3$, and $-\text{NHC}(=\text{O})\text{Ph}$. R^1 and R^2 may together form a cyclic structure, as in, for example, succinimidyl, maleimidyl, and phthalimidyl:



succinimidyl



maleimidyl



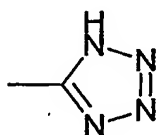
phthalimidyl

Thioamido (thiocarbamyl): $-C(=S)NR^1R^2$, wherein R^1 and R^2 are independently amino substituents, as defined for amino groups. Examples of amido groups include, but are not limited to, $-C(=S)NH_2$, $-C(=S)NHCH_3$, $-C(=S)N(CH_3)_2$, and $-C(=S)NHCH_2CH_3$.

Ureido: $-N(R^1)CONR^2R^3$ wherein R^2 and R^3 are independently amino substituents, as defined for amino groups, and R^1 is a ureido substituent, for example, hydrogen, a C_{1-7} alkyl group, a C_{3-7} heterocyclyl group, or a C_{5-7} aryl group, preferably hydrogen or a C_{1-7} alkyl group. Examples of ureido groups include, but are not limited to, $-NHCONH_2$, $-NHCONHMe$, $-NHCONHEt$, $-NHCONMe_2$, $-NHCONEt_2$, $-NMeCONH_2$, $-NMeCONHMe$, $-NMeCONHEt$, $-NMeCONMe_2$, and $-NMeCONEt_2$.

Guanidino: $-NH-C(=NH)NH_2$.

Tetrazolyl: a five membered aromatic ring having four nitrogen atoms and one carbon atom,



Amino: $-NR^1R^2$, wherein R^1 and R^2 are independently amino substituents, for example, hydrogen, a C_{1-7} alkyl group (also referred to as C_{1-7} alkylamino or di- C_{1-7} alkylamino), a C_{3-7}

heterocyclyl group, or a C₅₋₇ aryl group, preferably H or a C₁₋₇ alkyl group, or, in the case of a "cyclic" amino group, R¹ and R², taken together with the nitrogen atom to which they are attached, form a heterocyclic ring having from 4 to 8 ring atoms. Amino groups may be primary (-NH₂), secondary (-NHR¹), or tertiary (-NHR¹R²), and in cationic form, may be quaternary (-⁺NR¹R²R³). Examples of amino groups include, but are not limited to, -NH₂, -NHCH₃, -NHC(CH₃)₂, -N(CH₃)₂, -N(CH₂CH₃)₂, and -NHPh. Examples of cyclic amino groups include, but are not limited to, aziridino, azetidino, pyrrolidino, piperidino, piperazino, morpholino, and thiomorpholino.

Amidine (amidino): -C(=NR)NR₂, wherein each R is an amidine substituent, for example, hydrogen, a C₁₋₇ alkyl group, a C₃₋₇ heterocyclyl group, or a C₅₋₇ aryl group, preferably H or a C₁₋₇ alkyl group. Examples of amidine groups include, but are not limited to, -C(=NH)NH₂, -C(=NH)NMe₂, and -C(=NMe)NMe₂.

Nitro: -NO₂.

Nitroso: -NO.

Cyano (nitrile, carbonitrile): -CN.

Isocyano: -NC.

Thiocyano (thiocyanato): -SCN.

Sulfhydryl (thiol, mercapto): -SH.

Thioether (sulfide): -SR, wherein R is a thioether substituent, for example, a C₁₋₇ alkyl group (also referred

to as a C₁₋₇ alkylthio group), a C₃₋₇ heterocyclyl group, or a C₅₋₇ aryl group, preferably a C₁₋₇ alkyl group. Examples of C₁₋₇ alkylthio groups include, but are not limited to, -SCH₃ and -SCH₂CH₃.

5

Disulfide: -SS-R, wherein R is a disulfide substituent, for example, a C₁₋₇ alkyl group, a C₃₋₇ heterocyclyl group, or a C₅₋₇ aryl group, preferably a C₁₋₇ alkyl group (also referred to herein as C₁₋₇ alkyl disulfide). Examples of C₁₋₇ alkyl disulfide groups include, but are not limited to, -SSCH₃ and -SSCH₂CH₃.

15 Sulfine (sulfinyl, sulfoxide): -S(=O)R, wherein R is a sulfine substituent, for example, a C₁₋₇ alkyl group, a C₃₋₇ heterocyclyl group, or a C₅₋₇ aryl group, preferably a C₁₋₇ alkyl group. Examples of sulfine groups include, but are not limited to, -S(=O)CH₃ and -S(=O)CH₂CH₃.

20 Sulfone (sulfonyl): -S(=O)₂R, wherein R is a sulfone substituent, for example, a C₁₋₇ alkyl group, a C₃₋₇ heterocyclyl group, or a C₅₋₇ aryl group, preferably a C₁₋₇ alkyl group, including, for example, a fluorinated or perfluorinated C₁₋₇ alkyl group. Examples of sulfone groups include, but are not limited to, -S(=O)₂CH₃ (methanesulfonyl, mesyl), -S(=O)₂CF₃ (triflyl), -S(=O)₂CH₂CH₃ (esyl), -S(=O)₂C₄F₉ (nonafllyl), -S(=O)₂CH₂CF₃ (tresyl), -S(=O)₂CH₂CH₂NH₂ (tauryl), -S(=O)₂Ph (phenylsulfonyl, besyl), 4-methylphenylsulfonyl (tosyl), 4-chlorophenylsulfonyl (closyl), 4-bromophenylsulfonyl (brosyl), 4-nitrophenyl (nosyl), 2-naphthalenesulfonate (napsyl), and 5-dimethylamino-naphthalen-1-ylsulfonate (dansyl).

30

Sulfinic acid (sulfino): -S(=O)OH, -SO₂H.

Sulfonic acid (sulfo): $-S(=O)_2OH$, $-SO_3H$.

5 Sulfinate (sulfinic acid ester): $-S(=O)OR$; wherein R is a sulfinate substituent, for example, a C_{1-7} alkyl group, a C_{3-7} heterocyclyl group, or a C_{5-7} aryl group, preferably a C_{1-7} alkyl group. Examples of sulfinate groups include, but are not limited to, $-S(=O)OCH_3$ (methoxysulfinyl; methyl sulfinate) and $-S(=O)OCH_2CH_3$ (ethoxysulfinyl; ethyl sulfinate).

10

15 Sulfonate (sulfonic acid ester): $-S(=O)_2OR$, wherein R is a sulfonate substituent, for example, a C_{1-7} alkyl group, a C_{3-7} heterocyclyl group, or a C_{5-7} aryl group, preferably a C_{1-7} alkyl group. Examples of sulfonate groups include, but are not limited to, $-S(=O)_2OCH_3$ (methoxysulfonyl; methyl sulfonate) and $-S(=O)_2OCH_2CH_3$ (ethoxysulfonyl; ethyl sulfonate).

20 Sulfinyloxy: $-OS(=O)R$, wherein R is a sulfinyloxy substituent, for example, a C_{1-7} alkyl group, a C_{3-7} heterocyclyl group, or a C_{5-7} aryl group, preferably a C_{1-7} alkyl group. Examples of sulfinyloxy groups include, but are not limited to, $-OS(=O)CH_3$ and $-OS(=O)CH_2CH_3$.

25 Sulfonyloxy: $-OS(=O)_2R$, wherein R is a sulfonyloxy substituent, for example, a C_{1-7} alkyl group, a C_{3-7} heterocyclyl group, or a C_{5-7} aryl group, preferably a C_{1-7} alkyl group. Examples of sulfonyloxy groups include, but are not limited to, $-OS(=O)_2CH_3$ (mesylate) and $-OS(=O)_2CH_2CH_3$ (esylate).

30

Sulfate: $-OS(=O)_2OR$; wherein R is a sulfate substituent, for example, a C_{1-7} alkyl group, a C_{3-7} heterocyclyl group, or a C_{5-7} aryl group, preferably a C_{1-7} alkyl group. Examples of

sulfate groups include, but are not limited to, $-\text{OS}(=\text{O})_2\text{OCH}_3$ and $-\text{SO}(=\text{O})_2\text{OCH}_2\text{CH}_3$.

Sulfamyl (sulfamoyl; sulfinic acid amide; sulfinamide):

- 5 $-\text{S}(=\text{O})\text{NR}^1\text{R}^2$, wherein R^1 and R^2 are independently amino substituents, as defined for amino groups. Examples of sulfamyl groups include, but are not limited to, $-\text{S}(=\text{O})\text{NH}_2$, $-\text{S}(=\text{O})\text{NH}(\text{CH}_3)$, $-\text{S}(=\text{O})\text{N}(\text{CH}_3)_2$, $-\text{S}(=\text{O})\text{NH}(\text{CH}_2\text{CH}_3)$, $-\text{S}(=\text{O})\text{N}(\text{CH}_2\text{CH}_3)_2$, and $-\text{S}(=\text{O})\text{NHPh}$.

10

Sulfonamido (sulfinamoyl; sulfonic acid amide; sulfonamide):

- $-\text{S}(=\text{O})_2\text{NR}^1\text{R}^2$, wherein R^1 and R^2 are independently amino substituents, as defined for amino groups. Examples of sulfonamido groups include, but are not limited to,
- 15 $-\text{S}(=\text{O})_2\text{NH}_2$, $-\text{S}(=\text{O})_2\text{NH}(\text{CH}_3)$, $-\text{S}(=\text{O})_2\text{N}(\text{CH}_3)_2$, $-\text{S}(=\text{O})_2\text{NH}(\text{CH}_2\text{CH}_3)$, $-\text{S}(=\text{O})_2\text{N}(\text{CH}_2\text{CH}_3)_2$, and $-\text{S}(=\text{O})_2\text{NHPh}$.

- Sulfamino: $-\text{NR}^1\text{S}(=\text{O})_2\text{OH}$, wherein R^1 is an amino substituent, as defined for amino groups. Examples of sulfamino groups
- 20 include, but are not limited to, $-\text{NHS}(=\text{O})_2\text{OH}$ and $-\text{N}(\text{CH}_3)\text{S}(=\text{O})_2\text{OH}$.

- Sulfonamino: $-\text{NR}^1\text{S}(=\text{O})_2\text{R}$, wherein R^1 is an amino substituent, as defined for amino groups, and R is a sulfonamino
- 25 substituent, for example, a C_{1-7} alkyl group, a C_{3-7} heterocyclyl group, or a C_{5-7} aryl group, preferably a C_{1-7} alkyl group. Examples of sulfonamino groups include, but are not limited to, $-\text{NHS}(=\text{O})_2\text{CH}_3$ and $-\text{N}(\text{CH}_3)\text{S}(=\text{O})_2\text{C}_6\text{H}_5$.

- 30 Sulfinamino: $-\text{NR}^1\text{S}(=\text{O})\text{R}$, wherein R^1 is an amino substituent, as defined for amino groups, and R is a sulfinamino substituent, for example, a C_{1-7} alkyl group, a C_{3-7} heterocyclyl group, or a C_{5-7} aryl group, preferably a C_{1-7}

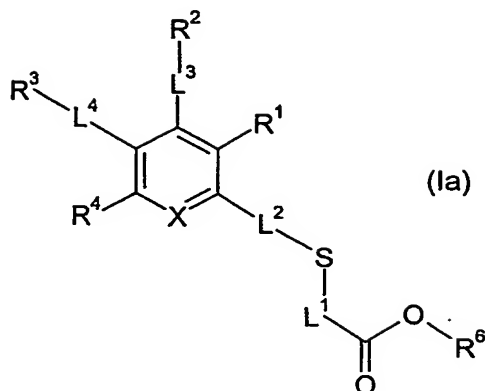
alkyl group. Examples of sulfinamino groups include, but are not limited to, =NHS(=O)CH_3 and $\text{-N(CH}_3\text{)S(=O)C}_6\text{H}_5$.

Includes Other Forms

- 5 Unless otherwise specified, included in the above are the well known ionic, salt, solvate, and protected forms of these substituents. For example, a reference to carboxylic acid (-COOH) also includes the anionic (carboxylate) form (-COO^-), a salt or solvate thereof, as well as conventional
- 10 protected forms such as esters. Similarly, a reference to an amino group includes the protonated form ($\text{-N}^+\text{HR}^1\text{R}^2$), a salt or solvate of the amino group, for example, a hydrochloride salt, as well as conventional protected forms of an amino group. Similarly, a reference to a hydroxyl
- 15 group also includes the anionic form (-O^-), a salt or solvate thereof, as well as conventional protected forms of a hydroxyl group.

Ester derivatives

- 20 The carboxylic acid moiety of compounds of formula I may be protected as an ester for example, as an optionally substituted C_{1-7} alkyl ester (e.g. a methyl ester; a t-butyl ester; a chloroethyl ester); an optionally substituted C_{5-6} aryl ester (e.g. a phenyl ester; a chlorophenyl ester; a
- 25 tolyl ester); or an optionally substituted C_{1-4} alkylene- C_{5-6} aryl ester (e.g., a benzyl ester; a nitrobenzyl ester). Thus included in the above are compounds of formula Ia:



wherein R¹, R², R³, R⁴, L¹, L², L³ and L⁴ are as defined above
 and R⁶ is selected from optionally substituted C₁₋₇ alkyl, C₅₋₆
 5 aryl and C₁₋₄ alkylene-C₅₋₆ aryl.

C₁₋₄ alkylene-C₅₋₆ aryl: The term "C₁₋₄ alkylene-C₅₋₆ aryl", as
 used herein, pertains to a bidentate moiety comprising a C₁₋₄
 alkylene moiety, -C₁₋₄ alkylene-, linked to a C₅₋₆ aryl
 10 moiety, -C₅₋₆ aryl, that is, -C₁₋₄ alkylene-C₅₋₆ aryl.

Examples of C₁₋₄ alkylene-C₅₋₆ aryl groups include, for
 example, methylene-phenyl (also known as benzyl), ethylene-
 phenyl, propylene-phenyl, and ethenylene-phenyl (also known
 15 as vinylene-phenylene).

The ester derivatives of formula Ia may function as prodrugs
 for the treatment of conditions alleviated by inhibition of
 glyoxalase I, i.e. proliferative conditions.

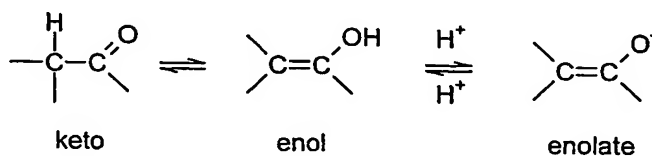
~~Isomers, Salts, Solvates and Protected Forms~~

Certain compounds may exist in one or more particular geometric, optical, enantiomeric, diastereomeric, epimeric, stereoisomeric, tautomeric, conformational, or anomeric forms, including but not limited to, cis- and trans-forms; E- and Z-forms; c-, t-, and r- forms; endo- and exo-forms; R-, S-, and meso-forms; D- and L-forms; d- and l-forms; (+) and (-) forms; keto-, enol-, and enolate-forms; syn- and anti-forms; synclinal- and anticlinal-forms; α - and β -forms; axial and equatorial forms; boat-, chair-, twist-, envelope-, and halfchair-forms; and combinations thereof, hereinafter collectively referred to as "isomers" (or "isomeric forms").

Note that, except as discussed below for tautomeric forms, specifically excluded from the term "isomers," as used herein, are structural (or constitutional) isomers (i.e., isomers which differ in the connections between atoms rather than merely by the position of atoms in space). For example, a reference to a methoxy group, $-\text{OCH}_3$, is not to be construed as a reference to its structural isomer, a hydroxymethyl group, $-\text{CH}_2\text{OH}$. Similarly, a reference to ortho-chlorophenyl is not to be construed as a reference to its structural isomer, meta-chlorophenyl. However, a reference to a class of structures may well include structurally isomeric forms falling within that class (e.g., C_{1-7} alkyl includes n-propyl and iso-propyl; butyl includes n-, iso-, sec-, and tert-butyl; methoxyphenyl includes ortho-, meta-, and para-methoxyphenyl).

The above exclusion does not pertain to tautomeric forms, for example, keto-, enol-, and enolate-forms, as in, for example, the following tautomeric pairs: keto/enol

(illustrated below), imine/enamine, amide/imino alcohol, amidine/amidine, nitroso/oxime, thioketone/enethiol, N-nitroso/hydroxyazo, and nitro/aci-nitro.



5

Note that specifically included in the term "isomer" are compounds with one or more isotopic substitutions. For example, H may be in any isotopic form, including ^1H , ^2H (D), and ^3H (T); C may be in any isotopic form, including ^{12}C , ^{13}C , and ^{14}C ; O may be in any isotopic form, including ^{16}O and ^{18}O ; and the like.

10

Unless otherwise specified, a reference to a particular compound includes all such isomeric forms, including (wholly or partially) racemic and other mixtures thereof. Methods for the preparation (e.g., asymmetric synthesis) and separation (e.g., fractional crystallisation and chromatographic means) of such isomeric forms are either known in the art or are readily obtained by adapting the methods taught herein, or known methods, in a known manner.

15

20

Unless otherwise specified, a reference to a particular compound also includes ionic, salt, solvate, and protected forms of thereof, for example, as discussed below.

25

It may be convenient or desirable to prepare, purify, and/or handle a corresponding salt of the active compound, for example, a pharmaceutically-acceptable salt. Examples of pharmaceutically acceptable salts are discussed in Berge et al., 1977, "Pharmaceutically Acceptable Salts," J. Pharm. Sci., Vol. 66, pp. 1-19.

30

For example, if the compound is anionic, or has a functional group which may be anionic (e.g., -COOH may be -COO^-), then a salt may be formed with a suitable cation. Examples of suitable inorganic cations include, but are not limited to, alkali metal ions such as Na^+ and K^+ , alkaline earth cations such as Ca^{2+} and Mg^{2+} , and other cations such as Al^{+3} . Examples of suitable organic cations include, but are not limited to, ammonium ion (i.e., NH_4^+) and substituted ammonium ions (e.g., NH_3R^+ , NH_2R_2^+ , NHR_3^+ , NR_4^+). Examples of some suitable substituted ammonium ions are those derived from: ethylamine, diethylamine, dicyclohexylamine, triethylamine, butylamine, ethylenediamine, ethanolamine, diethanolamine, piperazine, benzylamine, phenylbenzylamine, choline, meglumine, and tromethamine, as well as amino acids, such as lysine and arginine. An example of a common quaternary ammonium ion is $\text{N}(\text{CH}_3)_4^+$.

If the compound is cationic, or has a functional group which may be cationic (e.g., -NH_2 may be -NH_3^+), then a salt may be formed with a suitable anion. Examples of suitable inorganic anions include, but are not limited to, those derived from the following inorganic acids: hydrochloric, hydrobromic, hydroiodic, sulfuric, sulfurous, nitric, nitrous, phosphoric, and phosphorous.

Examples of suitable organic anions include, but are not limited to, those derived from the following organic acids: 2-acetyoxybenzoic, acetic, ascorbic, aspartic, benzoic, camphorsulfonic, cinnamic, citric, edetic, ethanedisulfonic, ethanesulfonic, fumaric, glucoheptonic, gluconic, glutamic, glycolic, hydroxymaleic, hydroxynaphthalene carboxylic, isethionic, lactic, lactobionic, lauric, maleic, malic, methanesulfonic, mucic, oleic, oxalic, palmitic, pantoic,

pantothenic, phenylacetic, phenylsulfonic, propionic, pyruvic, salicylic, stearic, succinic, sulfanilic, tartaric, toluenesulfonic, and valeric. Examples of suitable polymeric organic anions include, but are not limited to, those derived from the following polymeric acids: tannic acid, carboxymethyl cellulose.

It may be convenient or desirable to prepare, purify, and/or handle a corresponding solvate of the active compound. The term "solvate" is used herein in the conventional sense to refer to a complex of solute (e.g., active compound, salt of active compound) and solvent. If the solvent is water, the solvate may be conveniently referred to as a hydrate, for example, a mono-hydrate, a di-hydrate, a tri-hydrate, etc.

It may be convenient or desirable to prepare, purify, and/or handle the active compound in a chemically protected form. The term "chemically protected form" is used herein in the conventional chemical sense and pertains to a compound in which one or more reactive functional groups are protected from undesirable chemical reactions under specified conditions (e.g., pH, temperature, radiation, solvent, and the like). In practice, well known chemical methods are employed to reversibly render unreactive a functional group, which otherwise would be reactive, under specified conditions. In a chemically protected form, one or more reactive functional groups are in the form of a protected or protecting group (also known as a masked or masking group or a blocked or blocking group). By protecting a reactive functional group, reactions involving other unprotected reactive functional groups can be performed, without affecting the protected group; the protecting group may be removed, usually in a subsequent step, without substantially affecting the remainder of the molecule. See, for example,

Protective Groups in Organic Synthesis (T. Green and
P. Wuts; 3rd Edition; John Wiley and Sons, 1999).

A wide variety of such "protecting", "blocking", or
5 "masking" methods are widely used and well known in organic
synthesis. For example, a compound which has two
nonequivalent reactive functional groups, both of which
would be reactive under specified conditions, may be
derivatized to render one of the functional groups
10 "protected," and therefore unreactive, under the specified
conditions; so protected, the compound may be used as a
reactant which has effectively only one reactive functional
group. After the desired reaction (involving the other
functional group) is complete, the protected group may be
15 "deprotected" to return it to its original functionality.

For example, a hydroxy group may be protected as an ether
(-OR) or an ester (-OC(=O)R), for example, as: a t-butyl
ether; a benzyl, benzhydryl (diphenylmethyl), or trityl
20 (triphenylmethyl) ether; a trimethylsilyl or
t-butyldimethylsilyl ether; or an acetyl ester (-OC(=O)CH₃,
-OAc).

For example, an aldehyde or ketone group may be protected as
25 an acetal (R-CH(OR)₂) or ketal (R₂C(OR)₂), respectively, in
which the carbonyl group (>C=O) is converted to a diether
(>C(OR)₂), by reaction with, for example, a primary alcohol.

The aldehyde or ketone group is readily regenerated by
hydrolysis using a large excess of water in the presence of
30 acid.

For example, an amine group may be protected, for example,
as an amide (-NRCO-R) or a urethane (-NRCO-OR), for example,
as: a methyl amide (-NHCO-CH₃); a benzyloxy amide (-NHCO-

OCH₂C₆H₅, -NH-Cbz); as a t-butoxy amide (-NHCO-OC(CH₃)₃, -NH-Boc); a 2-biphenyl-2-propoxy amide (-NHCO-OC(CH₃)₂C₆H₄C₆H₅, -NH-Bpoc), as a 9-fluorenylmethoxy amide (-NH-Fmoc), as a 6-nitroveratryloxy amide (-NH-Nvoc), as a
5 2-trimethylsilylethyloxy amide (-NH-Teoc), as a 2,2,2-trichloroethyloxy amide (-NH-Troc), as an allyloxy amide (-NH-Alloc), as a 2(-phenylsulfonyl)ethyloxy amide (-NH-Psec); or, in suitable cases (e.g., cyclic amines), as a nitroxide radical (>N-O \cdot).

10

For example, a carboxylic acid group may be protected as an ester for example, as: an C₁₋₇ alkyl ester (e.g., a methyl ester; a t-butyl ester); a C₁₋₇ haloalkyl ester (e.g., a C₁₋₇ trihaloalkyl ester); a triC₁₋₇ alkylsilyl-C₁₋₇ alkyl ester;
15 or a C₅₋₇ aryl-C₁₋₇ alkyl ester (e.g., a benzyl ester; a nitrobenzyl ester); or as an amide, for example, as a methyl amide.

20

For example, a thiol group may be protected as a thioether (-SR), for example, as: a benzyl thioether; an acetamidomethyl ether (-S-CH₂NHC(=O)CH₃).

25

The term "treatment," as used herein in the context of treating a condition, pertains generally to treatment and
25 therapy, whether of a human or an animal (e.g., in veterinary applications), in which some desired therapeutic effect is achieved, for example, the inhibition of the progress of the condition, and includes a reduction in the rate of progress, a halt in the rate of progress,
30 amelioration of the condition, and cure of the condition. Treatment as a prophylactic measure (i.e., prophylaxis) is also included.

The term "therapeutically-effective amount," as used herein,

pertains to that amount of an active compound, or a material, composition or dosage from comprising an active compound, which is effective for producing some desired therapeutic effect, commensurate with a reasonable

- 5 benefit/risk ratio, when administered in accordance with a desired treatment regimen. Suitable dose ranges will typically be in the range of from 0.01 to 20 mg/kg/day, preferably from 0.1 to 10 mg/kg/day.

10 *Compositions and their administration*

- Compositions may be formulated for any suitable route and means of administration. Pharmaceutically acceptable carriers or diluents include those used in formulations suitable for oral, rectal, nasal, topical (including buccal and sublingual), vaginal or parenteral (including subcutaneous, intramuscular, intravenous, intradermal, intrathecal and epidural) administration. The formulations may conveniently be presented in unit dosage form and may be prepared by any of the methods well known in the art of pharmacy. Such methods include the step of bringing into association the active ingredient with the carrier which constitutes one or more accessory ingredients. In general the formulations are prepared by uniformly and intimately bringing into association the active ingredient with liquid carriers or finely divided solid carriers or both, and then, if necessary, shaping the product.
- 15
20
25

For solid compositions, conventional non-toxic solid carriers include, for example, pharmaceutical grades of mannitol, lactose, cellulose, cellulose derivatives, starch, magnesium stearate, sodium saccharin, talcum, glucose, sucrose, magnesium carbonate, and the like may be used. The active compound as defined above may be formulated as suppositories using, for example, polyalkylene glycols,

30

acetylated triglycerides and the like, as the carrier. Liquid pharmaceutically administrable compositions can, for example, be prepared by dissolving, dispersing, etc, an active compound as defined above and optional pharmaceutical adjuvants in a carrier, such as, for example, water, saline aqueous dextrose, glycerol, ethanol, and the like, to thereby form a solution or suspension. If desired, the pharmaceutical composition to be administered may also contain minor amounts of non-toxic auxiliary substances such as wetting or emulsifying agents, pH buffering agents and the like, for example, sodium acetate, sorbitan monolaurate, triethanolamine sodium acetate, sorbitan monolaurate, triethanolamine oleate, etc. Actual methods of preparing such dosage forms are known, or will be apparent, to those skilled in this art; for example, see Remington's Pharmaceutical Sciences, Mack Publishing Company, Easton, Pennsylvania, 15th Edition, 1975. The composition or formulation to be administered will, in any event, contain a quantity of the active compound(s) in an amount effective to alleviate the symptoms of the subject being treated.

Dosage forms or compositions containing active ingredient in the range of 0.25 to 95% with the balance made up from non-toxic carrier may be prepared.

For oral administration, a pharmaceutically acceptable non-toxic composition is formed by the incorporation of any of the normally employed excipients, such as, for example, pharmaceutical grades of mannitol, lactose, cellulose, cellulose derivatives, sodium crosscarmellose, starch, magnesium stearate, sodium saccharin, talcum, glucose, sucrose, magnesium, carbonate, and the like. Such compositions take the form of solutions, suspensions, tablets, pills, capsules, powders, sustained release

formulations and the like. Such compositions may contain 1%-95% active ingredient, more preferably 2-50%, most preferably 5-8%.

5 Parenteral administration is generally characterized by injection, either subcutaneously, intramuscularly or intravenously. Injectables can be prepared in conventional forms, either as liquid solutions or suspensions, solid forms suitable for solution or suspension in liquid prior to
10 injection, or as emulsions. Suitable excipients are, for example, water, saline, dextrose, glycerol, ethanol or the like. In addition, if desired, the pharmaceutical compositions to be administered may also contain minor amounts of non-toxic auxiliary substances such as wetting or
15 emulsifying agents, pH buffering agents and the like, such as for example, sodium acetate, sorbitan monolaurate, triethanolamine oleate, triethanolamine sodium acetate, etc.

The percentage of active compound contained in such parental
20 compositions is highly dependent on the specific nature thereof, as well as the activity of the compound and the needs of the subject. However, percentages of active ingredient of 0.1% to 10% in solution are employable, and will be higher if the composition is a solid which will be
25 subsequently diluted to the above percentages. Preferably, the composition will comprise 0.2-2% of the active agent in solution.

Acronyms

30 For convenience, many chemical moieties are represented using well known abbreviations, including but not limited to, methyl (Me), ethyl (Et), n-propyl (nPr), iso-propyl (iPr), n-butyl (nBu), sec-butyl (sBu), iso-butyl (iBu), tert-butyl (tBu), n-hexyl (nHex), cyclohexyl (cHex), phenyl

(Ph), biphenyl (biPh), benzyl (Bn), naphthyl (naph), methoxy (MeO), ethoxy (EtO), benzoyl (Bz), and acetyl (Ac).

For convenience, many chemical compounds are represented using well known abbreviations, including but not limited to, methanol (MeOH), ethanol (EtOH), iso-propanol (i-PrOH), methyl ethyl ketone (MEK), ether or diethyl ether (Et₂O), acetic acid (AcOH), dichloromethane (methylene chloride, DCM), acetonitrile (ACN), trifluoroacetic acid (TFA), dimethylformamide (DMF), tetrahydrofuran (THF), and dimethylsulfoxide (DMSO).

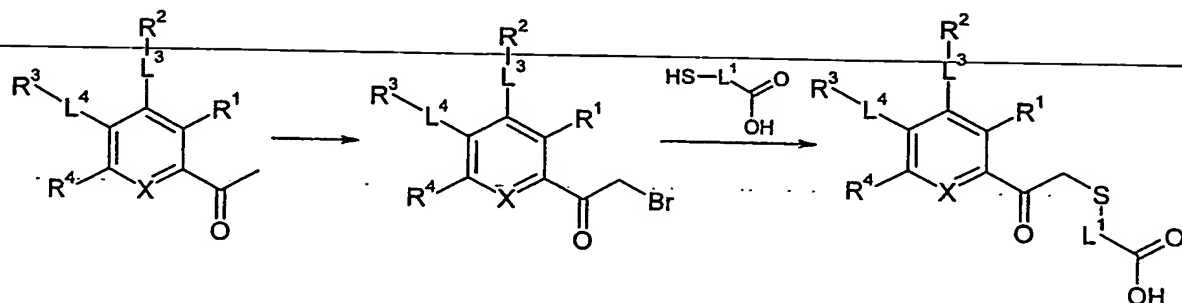
General Synthesis Method

Methods for the chemical synthesis of compounds of the present invention are described herein. These methods may be modified and/or adapted in known ways in order to facilitate the synthesis of additional compounds within the scope of the present invention. Descriptions of general laboratory methods and procedures, useful for the preparation of the compounds of the present invention, are described in Vogel's Textbook of Practical Organic Chemistry (5th edition, Ed. Furniss, B.S., Hannaford, A.J., Smith, P.W.G., Tatchell, A.R., Longmann, UK).

In the methods described below, other substituent groups to those introduced may be present as precursors of those groups, or as protected versions of those groups.

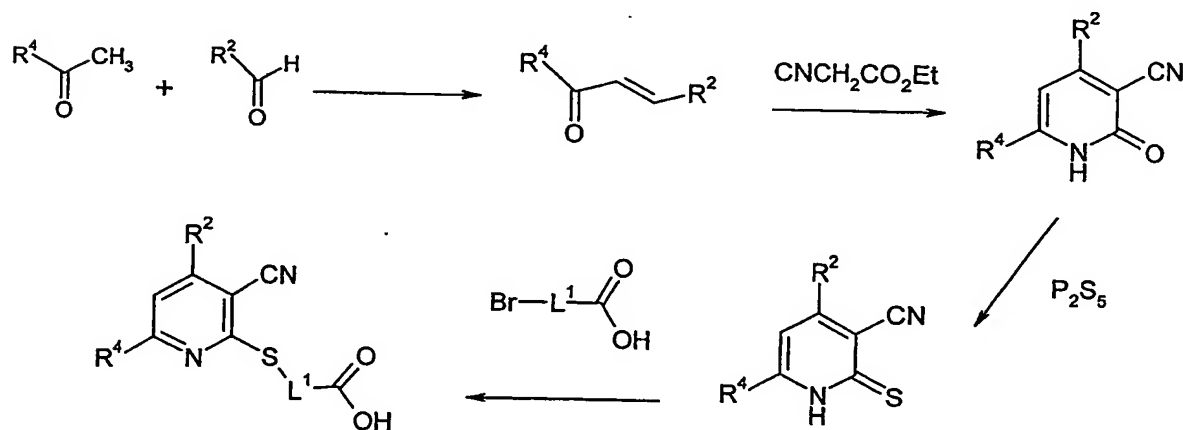
Compounds of formula I where L² is -C(=O)-CH₂-, can be synthesised according to the route shown in Scheme 1.

Scheme 1



Compounds of formula I where X is N, L₂ is a single bond, R₁ = CN and R₃ = H can be synthesised according to the route
 5 based on those disclosed in Manna *et al.*, *Bioorg. Med. Chem. Lett.* **10**, 1883-1885 (2000) and Salman, *Pharmazie* **54**, 178-183 (1999) (scheme 2).

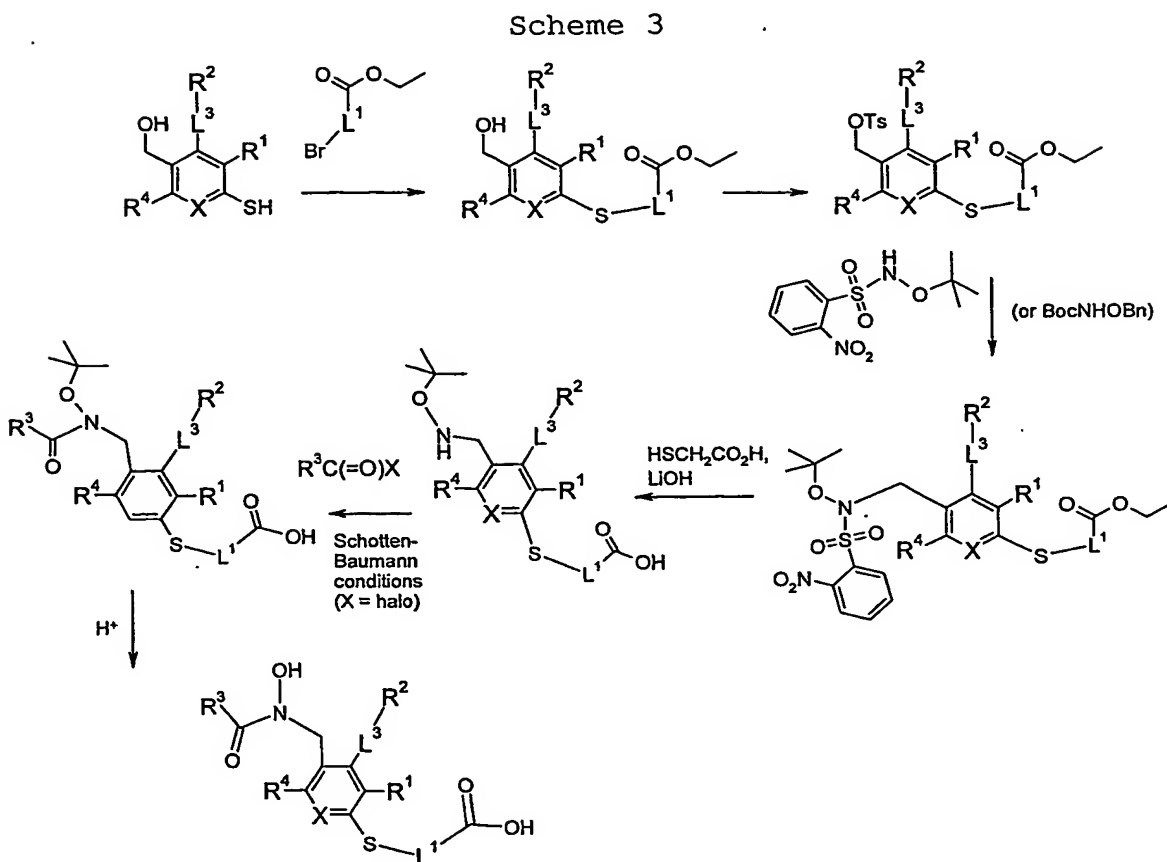
Scheme 2.



10 (X = N, L² = single bond, R¹ = CN, R³ = H)

Compounds of formula I where L₂ is a single bond and L₄ = -CH₂N(OH)C(=O)- can be synthesised according to the route
 based on that shown in Scheme 3. Compounds of formula I
 15 where L₂ is a single bond and L₃ = -CH₂N(OH)C(=O)- can also be synthesised by a route based on that shown in Scheme 3, except that the starting material comprises a hydroxymethyl group present in the *meta* position relative to the thiol

group, rather than in the *para* position as shown in scheme 3.



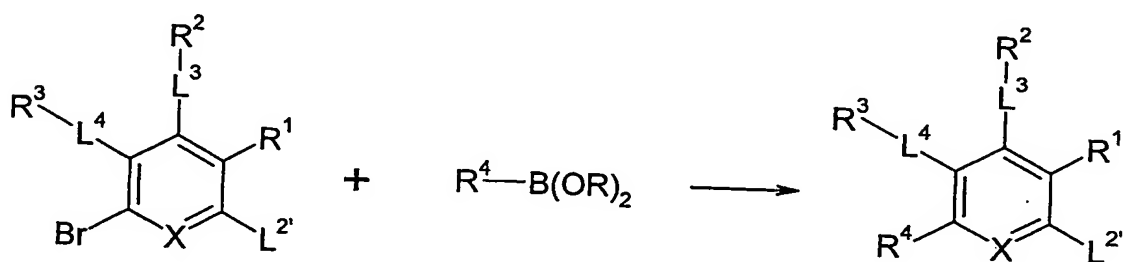
As shown in the above three schemes, the sulfur atom between L^2 and L^1 may be introduced as a nucleophilic attacking group (scheme 1) or by replacement (scheme 2), or may be present in the starting material (scheme 3).

In general, the group R^1 can be derived using standard reactions for the conversion of aryl substituent groups, including alkylation, reduction and substitution.

If R^3 and R^4 form a fused ring, then this would be present in the starting materials of a synthesis route to the compounds of the present invention.

When R^4 is an aryl or heterocyclyl group, this may be introduced to the compound by means of Suzuki coupling, i.e. by the coupling of an aryl halide to an organoboron derivative (scheme 4, wherein $L^{2'}$ indicates $-L^2-S-L^1-CO_2H$, or a precursor or protected form thereof and R is aryl or alkyl):

Scheme 4



10

A similar approach may be used to couple R^3 and R^2 to the central ring, when L^4 and L^3 respectively are single bonds. Furthermore, if R^2 or R^3 are aryl groups, the appropriate aryl halides may be coupled to boron derivatives of the remainder of the compound.

15

Certain compounds of the present invention are commercially available or can be derived from such compounds.

20 Preferences

The following preferences may be combined with one another, and may be different for each aspect of the present invention.

25 R^1 is preferably H, cyano, methyl, halo, hydroxy, hydroxamic acid, methoxy, amino, methylamino, dimethylamino, nitro, sulfhydryl, or methyl sulfide.

More preferably R^1 is cyano, H or hydroxamic acid.

Preferably L^1 is phenylene, methylene, ethylene, $-\text{CH}(\text{CH}_3)-$, $-\text{CH}(\text{iPr})-$, $-\text{CH}(\text{Ph})-$, $-\text{CH}_2\text{-phenylene-}$, $-\text{CH}_2\text{C(=O)NHCH}_2-$ or $-\text{CH}_2\text{C(=O)NH-phenylene-}$.

5

Preferably L^2 is a single bond or $-\text{C(=O)CH}_2-$.

Preferably L^3 is a single bond, $-\text{L}^9\text{YN(OH)C(=O)L}^{10}-$ or $-\text{L}^9\text{C(=O)N(OH)YL}^{10}-$, wherein L^9 and L^{10} are independently
10 selected from optionally substituted C_{1-4} alkylene, C_{5-6} arylene, C_{1-4} alkylene- C_{5-6} arylene and a single bond, and wherein Y is NH or a single bond.

Preferably L^4 is a single bond, $-\text{L}^9\text{YN(OH)C(=O)L}^{10}-$ or
15 $-\text{L}^9\text{C(=O)N(OH)YL}^{10}-$, wherein L^9 and L^{10} are independently selected from optionally substituted C_{1-4} alkylene, C_{5-6} arylene, C_{1-4} alkylene- C_{5-6} arylene and a single bond, and wherein Y is NH or a single bond.

20 For example, L^3 or L^4 may be a single bond, $-\text{CH}_2\text{N(OH)C(=O)-}$, $-\text{phenylene-CH}_2\text{N(OH)C(=O)-}$, $-\text{phenylene-NHN(OH)C(=O)-}$, or $-\text{CH}_2\text{C(=O)N(OH)-}$.

When X is CH, preferably one or more of R^1 , R^2 and R^4 are H.
25 More preferably two of R^1 , R^2 and R^4 are H, when X is CH. It is most preferred that all of R^1 , R^2 and R^4 are H, when X is CH.

When X is CH, preferably one of R^2 and R^3 is optionally
30 substituted C_{5-6} aryl, C_{3-7} cycloalkyl or C_{5-7} heterocyclyl. More preferably, when X is CH, R^3 is optionally substituted C_{5-6} aryl, C_{3-7} cycloalkyl or C_{5-7} heterocyclyl. It is most preferred that when X is CH, R^3 is optionally substituted phenyl or C_{3-7} cycloalkyl. For example, R^3 may be phenyl or

cyclopentyl.

When X is CH, preferably L^1 is phenylene or $-\text{CH}(\text{Ph})-$.

- 5 When X is CH, preferably one of L^3 and L^4 is a single bond. More preferably, when X is CH, L^3 is a single bond.

- When X is CH, preferably one of L^3 and L^4 is $-\text{L}^9\text{YN}(\text{OH})\text{C}(=\text{O})\text{L}^{10}-$ or $-\text{L}^9\text{C}(=\text{O})\text{N}(\text{OH})\text{YL}^{10}-$, wherein L^9 and L^{10} are independently selected from optionally substituted C_{1-4} alkylene, C_{5-6} arylene, C_{1-4} alkylene- C_{5-6} arylene and a single bond, and wherein Y is NH or a single bond. More preferably, when X is CH, L^4 is $-\text{L}^9\text{YN}(\text{OH})\text{C}(=\text{O})\text{L}^{10}-$ or $-\text{L}^9\text{C}(=\text{O})\text{N}(\text{OH})\text{YL}^{10}-$, wherein L^9 and L^{10} are independently selected from optionally substituted C_{1-4} alkylene, C_{5-6} arylene, C_{1-4} alkylene- C_{5-6} arylene and a single bond, and wherein Y is NH or a single bond.
- 10
- 15

When X is N, R^1 is preferably CN or hydroxamic acid.

20

- When X is N, R^2 is preferably selected from optionally substituted C_{5-6} aryl, C_{5-7} heterocyclyl, CF_3 and, together with R^3 , an optionally substituted butylene group wherein L^3 and L^4 are single bonds thus forming a C_6 ring fused with the aromatic ring to which L^3 and L^4 are attached.
- 25

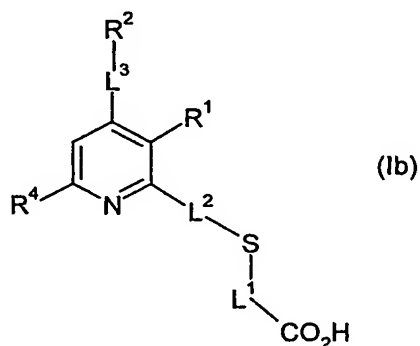
When X is N, R^2 is more preferably selected from optionally substituted C_{5-6} aryl and C_{5-7} heterocyclyl.

- 30 When X is N, R^2 is even more preferably optionally substituted phenyl or thiophenyl. For example, when X is N, R^2 may be thiophenyl, phenyl, *p*-chlorophenyl, *p*-methoxyphenyl, *o*-methoxyphenyl, *p*-fluorophenyl. When X is N and R^2 is a monosubstituted phenyl, it is preferred that R^2

is a parasubstituted phenyl.

When X is N preferably R³ is H or, together with R², an optionally substituted butylene group wherein L³ and L⁴ are single bonds thus forming a C₆ ring fused with the aromatic ring to which L³ and L⁴ are attached.

When X is N, it is more preferable that R³ is H and L⁴ is a single bond such that the compounds of the invention are of formula Ib.



When X is N, R⁴ is preferably selected from optionally substituted C₅₋₆ aryl and C₅₋₇ heterocyclyl. When X is N, R⁴ is more preferably optionally substituted phenyl, thiophenyl, furanyl or pyridyl. For example, when X is N R⁴ may be phenyl, *p*-tolyl, *p*-chlorophenyl, *p*-methoxyphenyl, 3,4-dimethoxyphenyl, *p*-fluorophenyl, thiophenyl, furanyl or pyridyl. When X is N and R⁴ is a monosubstituted phenyl, it is preferable that R⁴ is a parasubstituted phenyl. When X is N and R⁴ is a disubstituted phenyl, it is preferred that the substituents are in the *meta* and *para* positions.

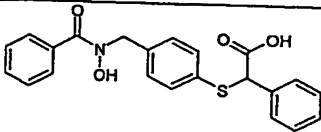
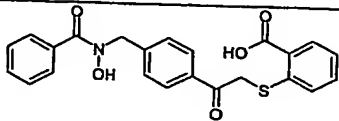
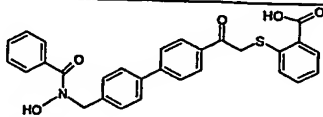
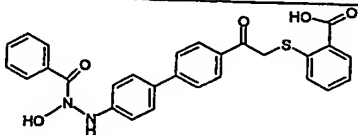
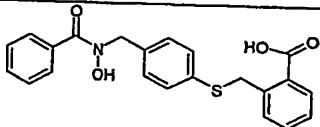
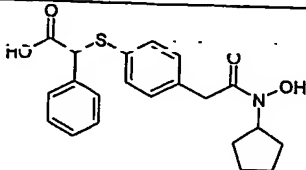
When R², R³ or R⁴ is a substituted C₅₋₆ aryl group, preferred substituents are halo, C₁₋₄ alkyl or -OR, wherein R is C₁₋₄ alkyl. When R², R³ or R⁴ is a monosubstituted phenyl group it

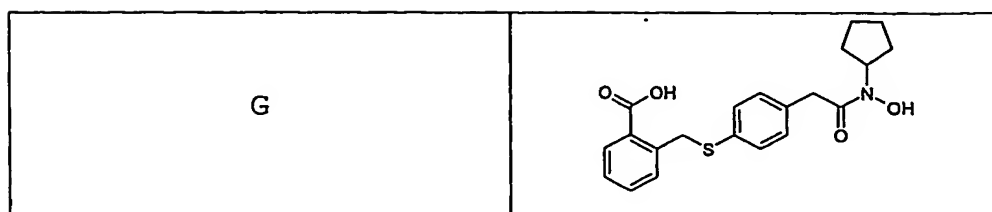
is preferred that the substituent is in the *para* position.

When R^2 , R^3 or R^4 is a disubstituted phenyl group it is preferred that the substituents are in the *para* and *meta* positions. For example R^2 , R^3 and R^4 may be *p*-tolyl, *p*-chlorophenyl, *p*-methoxyphenyl, 3,4-dimethoxyphenyl, *p*-fluorophenyl.

Particularly preferred compounds include those listed in tables 1 and 2.

Table 1

Compound	Structure
A	
B	
C	
D	
E	
F	



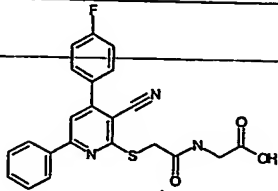
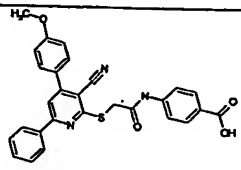
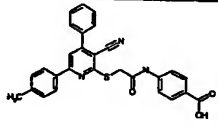
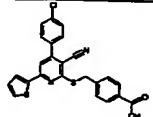
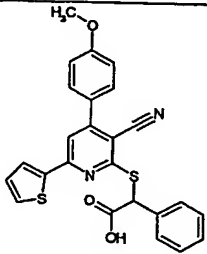
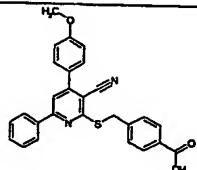
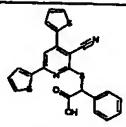
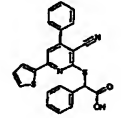
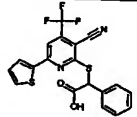
Examples

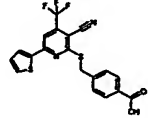
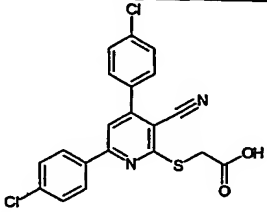
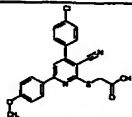
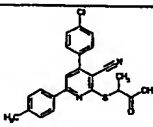
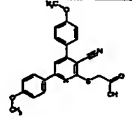
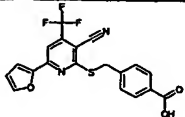
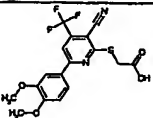
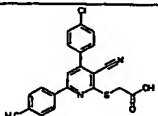
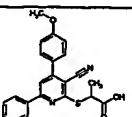
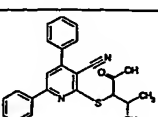
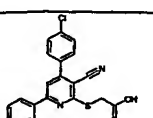
The compounds of table 2 were obtained from commercial sources.

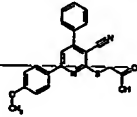
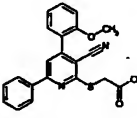
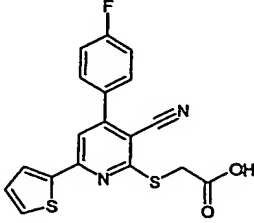
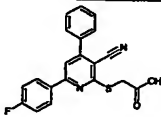
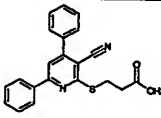
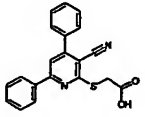
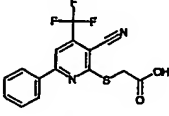
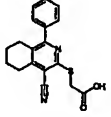
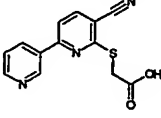
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Table 2

Compound	Structure
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The activity of such compounds for the inhibition of glyoxalase I can be assessed using the following assay method.

Glyoxalase I inhibition assay

Glyoxalase I catalyses the formation of S-D-lactoylglutathione from the hemithioacetal that forms non-enzymatically from methylglyoxal and reduced glutathione (GSH). The standard literature assay is a cuvette-based spectrophotometric method using the product of glyoxalase I, S-D-lactoylglutathione, as the chromophore (240 nm) (Racker, *J. Biol. Chem.* **190**, 685-686 (1951); Principato et al., *Biochem International* **6**, 249-255 (1983)). This literature method was modified for use as a 96-well plate, kinetic assay.

The buffer (0.1M potassium phosphate buffer pH 6.6) and inhibitors are added to appropriate wells of a 96 well plate. Methylglyoxal (prepared in potassium phosphate buffer pH 6.6) and reduced glutathione (prepared in potassium phosphate buffer pH 6.6) are added to appropriate wells. These reagents are incubated for 15 minutes, shaking at room temperature to allow the formation of the hemithioacetal substrate of glyoxalase I. Recombinant human glyoxalase I (expressed in *E. coli*. and purified by S-hexylglutathione-agarose chromatography as described in Ridderstorm M. and Mannervik B., *Biochem J.* **314**, 463-467 (1996)) is added and the plate is shaken briefly, before being placed in a Spectra Max 190 microplate spectrophotometer (Molecular Devices) at 25°C. Absorbance is monitored at 240 nm, with readings being taken every 30 seconds. The reaction is monitored for 15 minutes and PathCheck® measurements are taken on completion of the assay and the absorbance values normalized to a 1 cm pathlength. The integral software determines the Vmax using the first 20 readings. S-hexylglutathione is used as a positive control in the assays.

Data are expressed as a percentage of the control Vmax, measured in the absence of inhibitor.

5 Example 1

Various compounds from table 2 were subjected to the above glyoxalase I binding assay at a concentration of 20 μ M (20 micromolar). The following compounds exhibited inhibition, at 20 μ M, of 30% or above: 1,2,3,4,9,11,13,14,25.

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